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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/033,526	11/02/2001	Yadong Huang	UCAL217	7367

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EXAMINER
NICHOLS, CHRISTOPHER J

ART UNIT	PAPER NUMBER
1647	12

DATE MAILED: 08/08/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/033,526	HUANG ET AL.	
	Examiner	Art Unit	
	Christopher Nichols, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 May 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-38* is/are pending in the application.

4a) Of the above claim(s) *7-22, 25-27, 29-30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,23,24,28 and 31-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *2 November 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4)☒ Interview Summary (PTO-413) Paper No(s). *11* .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other:

DETAILED ACTION

Status of Application, Amendments, And/Or Claims

1. The amendment filed 21 May 2003 (Paper No. 10) has been entered in full. Claims **1, 23, 28,** and **31** have been amended and claims **32-38** have been added. Claims **1-6, 23, 24, 28,** and **31-38** are under examination.

2. Claims **7-22, 25-27,** and **29-30** remain withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Withdrawn Objections And/Or Rejections

4. The objections to the specification regarding informalities as set forth at pp. 3 ¶4-6 of the previous Office Action (Paper No. 9, 24 January 2003) is *withdrawn* in view of Applicant's amendments (Paper No. 10, 21 May 2003).

5. The rejection of claim **1** under 35 U.S.C. §112 ¶2 as set forth at pp. 3 ¶4-6 of the previous Office Action (Paper No. 9, 24 January 2003) is *withdrawn* in view of Applicant's amendments (Paper No. 10, 21 May 2003).

6. The rejection of claims **1-6** and **28** under 35 U.S.C. §102(b) as set forth at pp. 4-5 ¶8 of the previous Office Action (Paper No. 9, 24 January 2003) is *withdrawn* in view of Applicant's amendments (Paper No. 10, 21 May 2003).

7. The rejection of claims **23** and **24** under 35 U.S.C. §102(b) as set forth at pp. 5 ¶9 of the previous Office Action (Paper No. 9, 24 January 2003) is *withdrawn* in view of Applicant's amendments (Paper No. 10, 21 May 2003).

8. The rejection of claim **31** under 35 U.S.C. §102(b) as set forth at pp. 5-6 ¶10 of the previous Office Action (Paper No. 9, 24 January 2003) is *withdrawn* in view of Applicant's amendments (Paper No. 10, 21 May 2003).

New Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims **1-6, 23, 24,** and **31-38** are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *a method of inhibiting formation of neurofibrillary tangles said method comprising administering an agent selected from a group consisting of the following SEQ ID NO: 1, 3, and 4 wherein said agent reduces the formation of a neurotoxic carboxyl-terminal truncated form of apoE in a neuron wherein the carboxyl-terminal truncated apoE comprises amino acids 244-260 of apoE, wherein formation of neurofibrillary tangles is inhibited*, does not reasonably provide enablement for *practicing said method using other agents*.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

10. The above invention is drawn to a method of inhibiting formation of neurofibrillary tangles said method comprising administering an agent that reduces the formation of a neurotoxic carboxyl-terminal truncated form of apoE in a neuron wherein the carboxyl-terminal truncated apoE comprises amino acids 244-260 of apoE, and wherein formation of neurofibrillary tangles is inhibited. The language of said claims encompasses both *in vivo* and *in vitro* methods and the treatment of such diseases as Alzheimer's disease. The Specification shows in Figures 8 and 9 that the claimed peptides (SEQ ID NO: 1, 3, and 4) have the effect of reducing the formation of neurotoxic carboxy-terminal truncated apoE comprises amino acids 244-260 of apoE. However, no *in vivo* evidence is presented to demonstrate that the claimed peptides have an effect on the disclosed mouse models NSE-apoE3 and NSE-apoE4.

11. Said claims are drawn very broadly to include methods of treating individuals with diseases and disorders that involve pathogenic neurofibrillary tangles (NFT) using a broad range of possible agents. Since the specification fails to provide any guidance for the successful treatment of any known disease or disorders that involve pathogenic neurofibrillary tangles such as Alzheimer's disease, and since resolution of the various complications in regards to targeting the role of neurofibrillary tangles in diseases and disorders is highly unpredictable, one of skill in the art would have been unable to practice the invention without engaging in undue trial and error experimentation.

12. The specification as filed does not provide any guidance or examples that would enable a skilled artisan to use the disclosed methods of using agents other than SEQ ID NO: 1, 3, or 4 to

reduce NFT's in an individual. Additionally, a person skilled in the art would recognize that predicting the efficacy of using a poorly defined agent *in vivo* based solely on the performance of SEQ ID NO: 1, 3, and 4 *in vitro* as highly problematic. Thus, although the specification prophetically considers and discloses general methodologies of using the claimed methods with other agents *in vivo*, such a disclosure would not be considered enabling since the state of NFT's is highly unpredictable. The factors listed below have been considered in the analysis of enablement:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

13. The following references are cited herein to illustrate the state of the art of apoE, neurofibrillary tangles, and Alzheimer's disease.

14. On the breadth of the claims, the art recognizes that "agent" can pertain to chemical entities, pharmaceutical compositions, proteins, peptides, non-peptide compounds, animal tissue extracts, vegetable extracts, cell extracts, synthetic agents, biologically derived substances as well as proteinaceous substances, known, and unknown compounds (US 6046381 Col. 11 lines 35-67). Thus the claims which fail to recite limitations for what constitutes an applicable agent, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

15. On the nature of the invention, Bi *et al.* (17 July 2001) "Rapid induction of intraneuronal neurofibrillary tangles in Apolipoprotein E-deficient mice." PNAS **98**(15): 8832-8837 teaches that the administration of protease inhibitors, specifically lysosomal inhibitors, can actually augment the formation of neurofibrillary tangles (Figure 2). Since the claims are so broadly written, it is possible for agents which may meet the limitations of the claims to have other undesirable effects, such as augmenting NFT formation or apoE degradation by other enzymes creating other toxic apoE fragment.

16. More on the nature of the invention, Ljundberg *et al.* (7 May 2002) "Truncated apoE forms tangle-like structures in a neuronal cell line." Molecular Neuroscience **13**(6): 867-870 teaches that expression of apoE4 (d272-299) does not form neurofibrillary tangles but ring-like structures (pp. 870). Such structures are more reminiscent of aggresomes, a cellular defense mechanism against misfolded or foreign protein and no necessarily toxic {Kopito (December 2000) "Aggresomes, inclusion bodies and protein aggregation." Trends Cell Biol. **10**(12):524-30}. Thus the skilled artisan is confronted with conflicting interpretations of the role of the claimed apoE fragments. Further the skilled artisan is presented with an undue experimentation burden to determine if the claimed apoE fragments do indeed form NFT's and which agents are effective against their formation.

17. On the state of the prior art, no art was found discussing the role of carboxyl-terminal truncated apoE comprising amino acids 244-260 of apoE. Therefore the skilled artisan cannot rely on the prior art for guidance in practicing the invention.

18. Thus the specification of the instant application fails to provide adequate guidance for one of skill in the art to overcome the unpredictability and challenges of applying results from *in*

vitro experiments with SEQ ID NO: 1, 3, and 4 to other untested and undisclosed agents in *in vivo* treatment of NFT associated diseases and disorders as exemplified in the references above.

19. Furthermore, one skilled in the art would not accept on its face the examples given in the specification of the reduction of NFT's *in vitro* using SEQ ID NO: 1, 3, and 4 and the successful *in vivo* use other agents to treat NFT involved diseases and disorders. The specification as filed fails to provide any particular guidance which resolves the known unpredictability in the art associated with appropriate *in vivo* effects other agents on NFT's and specifically regarding the instant methods claimed.

20. In order to practice the invention using the specification and the state of the prior art as outlined above, the quantity of experimentation required to practice the invention as claimed *in vivo* would require the *de novo* determination of formulations with known NFT disease and disorders related signs and symptoms to correlate with relief due to administration of agents that have the desired inhibition of the formation of carboxyl-terminal truncated forms of apoE wherein the carboxyl-terminal truncated apoE comprises amino acids 244-260 of apoE. In the absence of any guidance from the specification, the amount of experimentation would be undue, and one would have been unable to practice the invention over the scope claimed.

21. Claim **28** is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

22. The above invention is drawn to a method of treating Alzheimer's disease via inhibiting the formation of neurofibrillary tangles said method comprising administering an inhibitor of a chymotrypsin-like serine protease in an amount effective to inhibit an enzyme that catalyzes the formation of carboxyl-terminal truncated apoE in a neuronal cell wherein the carboxyl-terminal truncated apoE comprises amino acids 244-260 of apoE, wherein the enzyme is inhibited, and wherein the enzyme is inhibited and the level of neurofibrillary tangles in a neuronal cell in the individual is reduced. The Specification shows in Figures 8 and 9 that the claimed peptides (SEQ ID NO: 1, 3, and 4) have the effect of reducing the formation of neurotoxic carboxyl-terminal truncated apoE comprises amino acids 244-260 of apoE. However, no *in vivo* evidence is presented to demonstrate that the claimed peptides have an effect on the disclosed mouse models NSE-apoE3 and NSE-apoE4. The Specification is also silent on the effect of agents that inhibit the formation of carboxyl-terminal truncated apoE in a neuronal cell wherein the carboxyl-terminal truncated apoE comprises amino acids 244-260 of apoE on Alzheimer's patients or Alzheimer's disease animal models (such as the PDAPP mouse).

23. Since the specification fails to provide any guidance for the successful treatment of Alzheimer's disease, and since resolution of the various complications in regards to Alzheimer's disease therapies is highly unpredictable, one of skill in the art would have been unable to practice the invention without engaging in undue trial and error experimentation.

24. The specification as filed does not provide any guidance or examples that would enable a skilled artisan to use the disclosed methods of using SEQ ID NO: 1, 3, or 4 to reduce NFT's in the neuronal cell of an individual thereby offering some relief from Alzheimer's disease. Additionally, a person skilled in the art would recognize that predicting the efficacy of using a

specific polypeptide *in vivo* based solely on its performance *in vitro* is highly problematic. Thus, although the specification prophetically considers and discloses general methodologies of using the claimed methods in *in vivo* therapeutic assays, such a disclosure would not be considered enabling since the state of Alzheimer's disease is highly unpredictable. The factors listed below have been considered in the analysis of enablement:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

25. The following references are cited herein to illustrate the state of the art of Alzheimer's disease.

26. On the breadth of the claims, the art recognizes that "agent" can pertain to chemical entities, pharmaceutical compositions, proteins, peptides, non-peptide compounds, animal tissue extracts, vegetable extracts, cell extracts, synthetic agents, biologically derived substances as well as proteinaceous substances, known, and unknown compounds (US 6046381 Col. 11 lines 35-67). Thus the claims which fail to recite limitations for what constitutes an applicable agent, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

27. On the nature of the invention, Bi *et al.* (17 July 2001) "Rapid induction of intraneuronal neurofibrillary tangles in Apolipoprotein E-deficient mice." PNAS **98**(15): 8832-8837 teaches that the administration of protease inhibitors, specifically lysosomal inhibitors, can actually

augment the formation of neurofibrillary tangles (Figure 2). Since the claims are so broadly written, it is possible for agents which may meet the limitations of the claims to have other undesirable effects, such as augmenting NFT formation or apoE degradation by other enzymes creating other toxic apoE fragment.

28. More on the nature of the invention, Ljundberg *et al.* (7 May 2002) "Truncated apoE forms tangle-like structures in a neuronal cell line." Molecular Neuroscience **13**(6): 867-870 teaches that expression of apoE4 (d272-299) does not form neurofibrillary tangles but ring-like structures (pp. 870). Such structures are more reminiscent of aggresomes, a cellular defense mechanism against misfolded or foreign protein and no necessarily toxic {Kopito (December 2000) "Aggresomes, inclusion bodies and protein aggregation." Trends Cell Biol. **10**(12):524-30}. Thus the skilled artisan is confronted with conflicting interpretations of the role of the claimed apoE fragments. Further the skilled artisan is presented with an undue experimentation burden to determine if the claimed apoE fragments do indeed form NFT's and which agents are effective against their formation.

29. On the state of the prior art, no art was found discussing the role of carboxyl-terminal truncated apoE comprising amino acids 244-260 of apoE. Therefore the skilled artisan cannot rely on the prior art for guidance in practicing the invention.

30. Thus the specification of the instant application fails to provide adequate guidance for one of skill in the art to overcome the unpredictability and challenges of applying results from *in vitro* experiments to the *in vivo* treatment of Alzheimer's disease as exemplified in the references above.

31. Furthermore, one skilled in the art would not accept on its face the examples given in the specification of the reduction of NFT's *in vitro* and the successful *in vivo* use these agents to treat Alzheimer's disease. The specification as filed fails to provide any particular guidance which resolves the known unpredictability in the art associated with appropriate *in vivo* effects of NFT's and specifically regarding the instant methods claimed.

32. In order to practice the invention using the specification and the state of the prior art as outlined above, the quantity of experimentation required to practice the invention as claimed *in vivo* would require the *de novo* determination of formulations with Alzheimer's disease to correlate with relief due to administration of agents that have the desired inhibition of the formation of carboxyl-terminal truncated forms of apoE wherein the carboxyl-terminal truncated apoE comprises amino acids 244-260 of apoE. In the absence of any guidance from the specification, the amount of experimentation would be undue, and one would have been unable to practice the invention over the scope claimed.

33. Claims **1, 2, 23, 28, 31,** and **32** are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

34. The claims are broadly drawn to agents and inhibitors that can inhibit the formation neurofibrillary tangles (NFT) *in vivo* and *in vitro*. In addition, the claims encompass therapy for Alzheimer's disease and any disorder which involves NFT. While the Specification provides

ample support for the use of SEQ ID NO: 1, 3, and 4 in this capacity it does not provide adequate written description of any other agents (including inhibitors) which have a similar activity. The art recognizes that "agent" can pertain to chemical entities, pharmaceutical compositions, proteins, peptides, non-peptide compounds, animal tissue extracts, vegetable extracts, cell extracts, synthetic agents, biologically derived substances as well as proteinaceous substances, known, and unknown compounds. Due to the large quantity of experimentation necessary to identify all the applicable agents, the lack of direction/guidance presented in the specification regarding synthesizing, screening, and evaluating all applicable agents, the absence of working examples directed to known agents, the complex nature of the invention, the unpredictability of the effects of agents on cells and the breadth of the claims which fail to recite limitations for what constitutes an applicable agent, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

35. Claims **33-38** are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "kD" in claims 33-38 is a relative term which renders the claim indefinite. The term "kD" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. kD values are determined by a number of experimental means, therefore, absent clear indication of the method by which the given kD

value is determined, the skilled artisan is not presented with an unambiguous measurement. It is noted that the Examiner has included proposed Amendments to obviate this rejection.

Summary

36. No claims are allowed.

37. The following amendments were suggested to the Applicant by the Examiner but *declined* on 14 July 2003.

38. Proposed claims amendments:

Claim 1 (Twice Amended) A method of inhibiting formation of neurofibrillary tangles in an individual, said method comprising: administering to the individual ~~an agent~~ a peptide that reduces formation of a neurotoxic carboxyl-terminal truncated apoE comprises amino acids 244-260 of apoE, wherein the peptide is 4 or 5 residues long, and wherein formation of neurofibrillary tangles is inhibited.

Claim 23 (Twice Amended) A method of inhibiting formation of neurofibrillary tangles in a neuronal cell of an individual, the method comprising: contacting the neuronal cell with ~~an agent~~ a peptide that inhibits an enzymatic activity of an enzyme in the neuronal cell that catalyzes cleavage of apoE in the cell to generate neurotoxic carboxyl-terminal truncated apoE, wherein the carboxyl-terminal truncated apoE comprises amino acids 244-260 of apoE, and wherein the peptide is 4 or 5 residues long.

Claim 24 (Amended) The method of claim 23, wherein the ~~agent is a~~ peptide is selected from the group consisting of Ala-Ala-Pro-Phe (SEQ ID NO: 1), Ala-Ala-Pro-Leu (SEQ ID NO: 3), and Ala-Ala-Ala-Ala-Pro-Phe (SEQ ID NO: 4).

Claim 28 (Twice Amended) A method of treating Alzheimer's disease, the method comprising" administering ~~an inhibitor of a chymotrypsin-like serine protease~~ a peptide selected from the group consisting of Ala-Ala-Pro-Phe (SEQ ID NO: 1), Ala-Ala-Pro-Leu (SEQ ID NO: 3), and Ala-Ala-Ala-Ala-Pro-Phe (SEQ ID NO: 4) in an amount effective to inhibit an enzyme that catalyzes the formation of carboxyl-terminal truncated apoE in a neuronal cell, wherein the carboxyl-terminal truncated apoE comprises amino acids 244-260 of apoE, and wherein the enzyme is inhibited and the level of neurofibrillary tangles in a neuronal cell in the individual is reduced.

Claim 31 (Twice Amended) A method of reducing the level of carboxyl-terminal truncated apoE in a neuronal cell, the method comprising: contacting the cell with ~~an agent~~ a peptide that reduces activation of an enzyme that catalyzes the formation of neurotoxic carboxyl-terminal truncated apoE in a neuronal cell, wherein said enzyme is activated by $A\beta_{1-42}$, wherein a reduction in the activation of the enzyme results in a reduction in the level of neurotoxic carboxyl-terminal truncated apoE in the cell, and wherein the peptide is 4 or 5 residues long.

Claim 33 (Amended) The method of claim 1, wherein the carboxyl-terminal truncated form of apoE has a molecular weight of from ~~about~~ 28 kD to ~~about~~ 39 kD as determined by SDS-PAGE analysis.

Claim 34 (Amended) The method of claim 1, wherein the carboxyl-terminal truncated form of apoE has a molecular weight of from ~~about~~ 14 kD to ~~about~~ 20 kD as determined by SDS-PAGE analysis.

Claim 35 (Amended) The method of claim 23, wherein the carboxyl-terminal truncated form of apoE has a molecular weight of from ~~about~~ 28 kD to ~~about~~ 39 kD as determined by SDS-PAGE analysis.

Claim 36 (Amended) The method of claim 23, wherein the carboxyl-terminal truncated form of apoE has a molecular weight of from ~~about~~ 14 kD to ~~about~~ 20 kD as determined by SDS-PAGE analysis.

Claim 37 (Amended) The method of claim 32, wherein the carboxyl-terminal truncated form of apoE has a molecular weight of from ~~about~~ 28 kD to ~~about~~ 39 kD as determined by SDS-PAGE analysis.

Claim 38 (Amended) The method of claim 32, wherein the carboxyl-terminal truncated form of apoE has a molecular weight of from ~~about~~ 14 kD to ~~about~~ 20 kD as determined by SDS-PAGE analysis.

Claim 39 (New) The method of claim 1, wherein the ~~agent is a~~ peptide is selected from the group consisting of Ala-Ala-Pro-Phe (SEQ ID NO: 1), Ala-Ala-Pro-Leu (SEQ ID NO: 3), and Ala-Ala-Ala-Ala-Pro-Phe (SEQ ID NO: 4).

Claim 40 (New) The method of claim 31, wherein the ~~agent is a~~ peptide is selected from the group consisting of Ala-Ala-Pro-Phe (SEQ ID NO: 1), Ala-Ala-Pro-Leu (SEQ ID NO: 3), and Ala-Ala-Ala-Ala-Pro-Phe (SEQ ID NO: 4).

39. The above amendments are included to be made of record.

40. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

GARY KUNZ
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Christopher James Nichols, Ph.D.** whose telephone number is 703-305-3955. The examiner can normally be reached on Monday through Friday, 8:00AM to 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Gary Kunz, Ph.D.** can be reached on 703-308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications. The fax phone numbers for the customer service center is 703-872-9305

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

CJN
August 7, 2003